Mittuniversitetet
MID SWEDEN UNIVERSITY

Thesis for the degree of Licentiate of Technology, Östersund 2016

SURFACE PROPERTIES OF IMPLANTS MANUFACTURED USING ELECTRON BEAM MELTING

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ISSN 1652-8948
Mid Sweden University Licentiate Thesis 122
ISBN 978-91-88025-49-4

Akademisk avhandling som med tillstånd av Mittuniversitetet framläggs till offentlig granskning för avläggande av teknologie licentiatexamen fredag, 22/1, 2016, klockan 10.15 i sal G1353, Mittuniversitetet Östersund.
Seminariet kommer att hållas på svenska.

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Printed by Mid Sweden University, Sweden, 2016

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ABSTRACT

This thesis summarizes the results concerning the manufacture of medical implants for bone replacement using electron beam melting (EBM) which is an additive manufacturing (AM) technology, and aims to satisfy the engineering needs for the medical functionality of manufacturing technology. This thesis has focused on some microscopic properties for surfaces and bone integration. The process parameters of EBM manufacturing were studied to ascertain whether they have impacts on surface appearance, as surface properties have impacts on bone integration and implant performance.

EBM manufacturing uses an electron beam to melt metal powder onto each layer in a manner akin to welding. The electron beam is controlled by process parameters that may be altered to a certain extent by the operator. There are individual process parameters for every material, and new parameters are set when developing new materials. In this thesis, process parameters in default settings were altered to ascertain whether it was possible to specify process parameters for implant manufacturing. The blood chamber model was used for thromboinflammation validation, using human whole blood. The model is used to identify early reactions of coagulation and immunoreactions. The material used in this study was Ti6Al4V-ELI, which is corrosion resistant and has the same surface oxide layers as titanium, and CoCr-F75, which has high stiffness, is wear-resistant and is commonly used in articulating joints.

The study shows that among the process parameters researched, a combination of speed and current have the most impact on surface roughness and an interaction of parameters were found using design of experiment (DOE). As-built EBM surfaces show thrombogenicity, which in previous studies has been associated with bone ingrowth.

Surface structure of as-build EBM manufactured surfaces are similar to implants surfaces described by Pilliar (2005), but with superior material properties than those of implants with sintered metals beads. By altering the process parameters controlling the electron beam, surface roughness of as-build parts may be affected, and the rougher EBM manufactured surfaces tend to be more thrombogen than the finer EBM manufactured surfaces. As-build EBM manufactured surfaces in general show more thrombogenicity than conventional machined implants surfaces.

Keywords: electron beam melting, blood coagulation, bone ingrowth, surface roughness, process parameters.

SAMMANFATTNING

Denna avhandling behandlar tillverkning av medicinska implantat för integration i ben. I fokus är den additiva tillverkningstekniken ”elektronstrålesmältning” (Electron Beam Melting –EBM), en av flera tekniker som populärt beskrivs med termen 3D-skrivare. Avhandlingen fokuserar på mikroskopiska ytegenskaper och dess inverkan på benintegration. Processparametrarna för EBM-tillverkning studerades för att fastställa hur de påverkar ytans utseende, efter som ytegenskaper har effekt på implantatens funktion.

EBM-tillverkning använder en elektronstråle som likt svetsning smälter ihop metallpulver. Elektronstrålen styrs av processparametrar som till viss mån kan justeras av maskinoperatören. Det finns individuella processparametrar för varje material och nya parametrar utvecklas till varje ny legering. I denna avhandling har ”grundinställningarnas processparametrar” studerats för att ta reda på om det är möjligt att ställa in specifika parametrar till implantattillverkning. Med hjälp av blodkammarmetoden, som använder humant blod, har thromboinflammatoriska egenskaper undersökts. Metoden identifierar tidiga koagulations- och immunologiska reaktioner. Legeringarna som undersökts i denna studie var Ti6Al4V-ELI, som är korrosionsbeständigt med samma uppsättning oxider på ytan som titan har, och CoCr-F75, en legering som har hög styvhet, är slitstarkt och är vanligt förekommande i implantat för leder.

Bland de undersökta processparametrarna visar en kombination av hastighet och ström ha mest inverkan på ytjämnhet och en interaktion mellan parametrar identifierades med hjälp av försöksplanering. EBM-tillverkade ytor visade på thrombogena egenskaper som i tidigare studier kan relateras till god integration i benvävnad.

Ytstrukturen hos EBM-tillverkade ytor liknar de implantatytor som Pilliar (2005) beskriver, men materialegenskaperna är bättre än de materialegenskaper som implantat, med sintrad yta, har. Genom att ändra processparametrarna som styr elektronstrålen kan ytstrukturen påverkas. Grövre EBM-tillverkade ytor tenderar att vara mer thrombogena än de finare EBM-tillverkade ytorna är. Obehandlade EBM-tillverkade ytor i allmänhet är mer thrombogena än vad konventionellt framställda implantatytor är.

TABLE OF CONTENTS

ABBREVIATIONS

3D	Three-dimensional
AFM	Atomic force microscopy
AM	Additive manufacturing
ASTM	ASTM International – an international standards organization
AT	Antithrombin
BCC	Body-centered cubic
C1-inh	Complement component 1 inhibitor
CoCr	Cobalt-Chromium ASTM F75 alloy
CP	Commercially pure
CT	Computed tomography
EBM	Electron beam melting
ELI	Extra-low interstitials
ELISA	Enzyme-linked immunosorbent assay
FIX	Coagulation factor IX
FV	Coagulation factor V
FVII	Coagulation factor VII
FVIII	Coagulation factor VIII
FX	Coagulation factor X
FXIa	Activated coagulation factor XI
FXIIa	Activated coagulation factor XII
HCP	Hexagonal close packed
HIP	Hot isostatic pressing
HMWK or HK	High molecular weight kininogen
HOM	Homogenization heat treatment
HRC	Rockwell C hardness
In vitro	Test tube experiment (Latin "in glass")
MRI	Magnetic resonance imaging
R_a	Average surface roughness
SEM	Scanning electron microscopy
TF	Tissue factor
Ti6Al4V	Titanium alloy with 6 (wt%) aluminum and 4 (wt%) vanadium

LIST OF PAPERS

This thesis is based primarily on the following four papers, herein referenced by their Roman numerals:

Paper I Electron Beam Melting: Moving from Macro- to Micro- and Nanoscale
Andrey Koptyug, Lars-Erik Rännar, Mikael Bäckström and Rebecca P. Klingvall
Materials Science Forum Vols. 706-709 (2012) pp 532-537

Paper II Blood Coagulation on Electron Beam Melted Implant Surfaces, Implications for Bone Ingrowth
Rebecca P. Klingvall, Jaan Hong and Slavko Dejanovic
24th European Conference on Biomaterials, September 4th–9th, Dublin 2011

Paper III The Effect of EBM Process Parameters upon Surface Roughness
Rebecca Ek, Lars-Erik Rännar, Mikael Bäckström and Peter Carlsson
Accepted for publication in Rapid Prototyping Journal

Paper IV Micro to macro roughness of additive manufactured titanium implants regarding coagulation and contact activation
Rebecca Ek, Jaan Hong, Andreas Thor, Mikael Bäckström, Lars-Erik Rännar.
Submitted

1. INTRODUCTION

1.1 Additive manufacturing

1.1.1 Industrial revolution?

Modern additive manufacturing (AM) equipment was launched in the 1980s (Noorani, 2006). The process uses a 3D computer model to manufacture products by adding layers of material on top of each other according to the computer model. This thesis mainly concerns the AM technique of electron beam melting (EBM). This manufacturing process will be described in the Materials and Methods section. In its early days, AM was used primarily for making prototypes, but the technology has been developing quickly alongside advances in computer hardware and software. Material properties are enhanced and new machines and new materials are developed continuously. New products and applications appear as materials continue to improve. Nowadays it is possible to buy 3D-printing equipment to use at home making chocolates, figures or toys for a reasonable amount of money.

The term AM is used by researchers and industry and is associated with expensive equipment, while 3D-printing is a term used by popular science and media to address cheap equipment. However, the term 3D-printing sometimes extends to AM equipment too. Society has an impact on the research development today, as movies and design industries drive the development of simple parts and universities and industries invent functioning products with good material properties. Using AM, supply and demand chains will be changed, in contrast to the export and importing paradigm of today. One example is the manufacturing of functioning tools in a space station, where the products do not have to be delivered, but rather someone simply has to deliver machines and raw material. Garrett (2014) states, "Policymakers need to embrace this new technology and prepare for its disruptive impact on the economy" and questions whether 3D-printing is a part of a third industrial revolution.

Sharing files and information through the Internet has allowed the music industry to go through major changes, making it possible for Spotify and iTunes, for example, to have large shares in the economy. How 3D-printing will affect the economy remains a question, but US President Barack Obama has stated that the revolution have already started (The White House Office of the Press Secretary, 2013).

Comparing the number of publications each year that involve titanium research and the number of publications that include the phrase "additive manufacturing," the correlation appears as nearly a straight line using a logarithmic y-axis scale (See Figure 1). The number of publications that include the phrase "additive manufacturing" has increased as much in the past 5 years as titanium research has in the past 15 years.

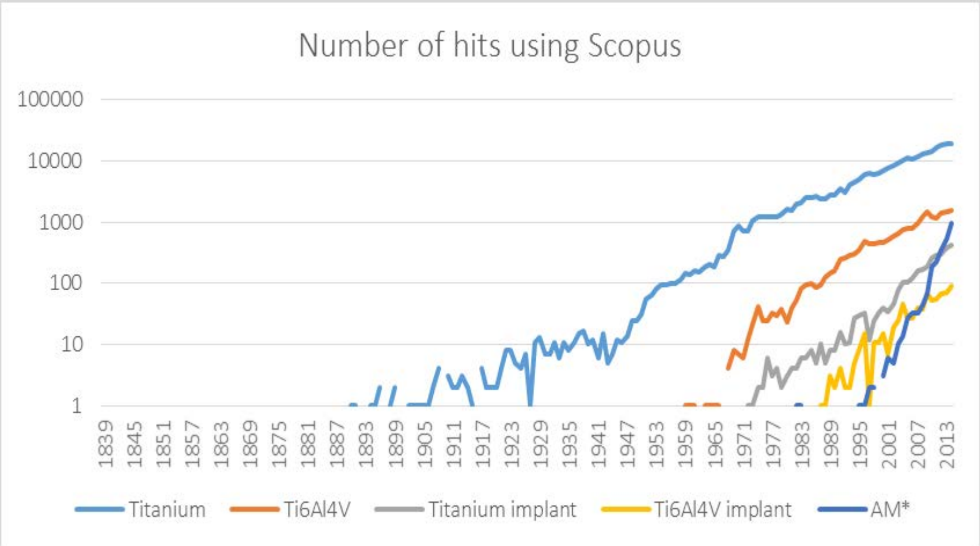

Figure 1. Number of publications hits each year using Scopus. * "additive manufacturing".

ASTM Committee F42 on Additive Manufacturing Technologies is the newest ASTM committee. The committee was formed in January 2009 and holds meetings twice a year. Their scope is, "The promotion of knowledge, stimulation of research and implementation of technology through the development of standards for additive manufacturing technologies"(ASTM International). One example of standards made for AM is ASTM F3001 – 14, which is a "Specification for Additive Manufacturing Titanium-6 Aluminum-4 Vanadium ELI (Extra Low Interstitial) with Powder Bed Fusion"(ASTM International).

Not only has manufacturing equipment developed, but also software has been designed to fit the demands posed by AM. Some software packages aim to extract anatomical data from CT or MRI scans, while others aim at printing science fiction figurines.

1.1.2 Material and functional properties

Metal AM production with fully melted material properties have been manufactured using a laser or electron beam for more than 10 years. Selective Laser Melting, for example, can manufacture Ti6Al4V-products from 5-50 μm of powder, using a layer thickness of 30 μm and a build atmosphere with non-reactive gas atmosphere e.g. argon-gas. Melting and solidification occur with a high temperature gradient, resulting in thermal stresses and non-equilibrium phases (Thijs *et al.*, 2010). EBM operates in a vacuum and fabricates products with material properties comparable to cast and wrought products (Svensson *et al.*, 2009). The pre-heating stage in the EBM process gives Ti6Al4V material properties of natural aging due to simultaneous global cooling after the build is done. EBM is used mostly by the medical implant and aerospace industries. There are few EBM materials to keep track of; currently there are only five alloys commercially available and these alloy compositions were all first invented for conventional manufacturing such as casting or machining. New alloys made specifically for EBM-manufacturing will be developed in the near future, and these alloys will have the potential to have better material properties and even tailored microstructures. Some examples are amorphous metal (AlphaGalileo, 2012) or titanium aluminides (Cormier *et al.*, 2008).

AM technology allows for products with new geometries which cannot be manufactured using conventional methods such as forging, welding and turning. New products with properties originating from new geometries can be manufactured using AM technology. An example is mesh structures with negative Poisson's ratios (Yang *et al.*, 2012). All mesh structures have high strength-to-density ratios and have material properties dependent on geometry. Another advantage is that there is little waste, which has economic advantages (Cronskär *et al.*, 2013).

AM can be used for small number batches or series production. AM will not replace conventional mass production, but new geometry products may be mass-produced. Some examples of new geometry products for series production are the acetabular cup with mesh structures that has been CE-marked since 2007 (Ohldin, 2010). Another example of new geometry mass production is from Airbus, which uses AM to manufacture cabin brackets and hinges out of titanium (See Figure 2).

Figure 2. Airbus is manufacturing cabin brackets and hinges out of titanium. (On 3D Printing)

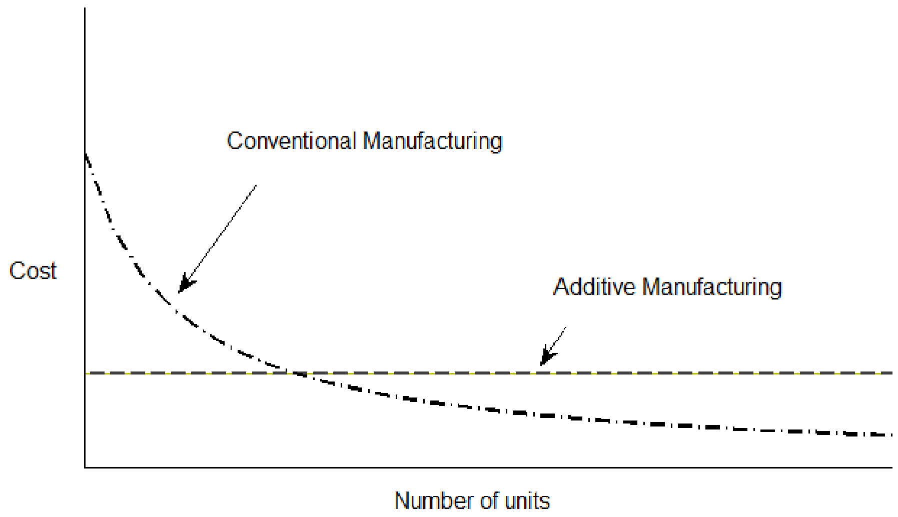

Figure 3. Graph showing number of units compared to cost.

In Figure 3, a schematic graph shows how the price of conventional manufacturing drops as the number of units increases, while costs for AM are more linear compared to number of units, which opens the door to small numbers of batches and customization. Single cases or small batches do not need any customized tools and it is fairly simple to prepare one model for production.

An issue of small batches and customized products is product verification. If there were a non-destructive verification method, it would increase the reliability of products. Medical implants that have been mass produced using EBM have CE-certification, but customized implants do not fit in the same scope, which makes it challenging to certify customized implants. New certification models have to be adapted to the growing market of customized implants.

Post-processing of EBM products is necessary to achieve a surface structure comparable to the conventional surfaces of machined or polished surfaces. The surface properties of as-built materials are much rougher compared to conventional machining, and typical surface roughness values are 20-50 μm. This thesis focuses on untreated EBM manufactured surfaces to investigate their properties for use in medical implants and bone integration.

1.2 Physiology

1.2.1 Titanium and biocompatibility

The term biocompatibility is often misused or even misunderstood. Some materials are good in one biological context but do not work at all in other applications, which is why it is important to constantly be reminded that biocompatibility has a very narrow spectrum and is only applicable with a specific application.

Most literature lists PI Brånemark as the founder of titanium implants, although there have been reports on titanium as bone anchorage material before by Bothe *et al.* (1940) and Leventhal (1951). Brånemark *et al.* (1977) published a ten-year study where 1618 titanium fixtures had been implanted. Since Brånemark discovered the phenomenon of osseointegration, titanium dental implants reached international recognition. Titanium has natural biocompatible properties for bone ingrowth. It has been considered biocompatible because of its lack of adverse reactions and therefore was considered bioinert. Hong *et al.* (1999) report titanium as a highly thrombogenic material, which is a property that seems to correlate well with good biocompatibility for bone ingrowth

1.2.2 Bone tissue

Bone is a living material, and its shape and density may change over time. Bone material can grow or be removed by resorption, and all material transportation is done via blood circulation. The shape and strength of a bone adapts according to mechanical stress distribution over time. Julius Wolff first proposed this idea in 1884 (Wolff, 2010), and Pauwels (1948) showed that the structure of spongy bone follows a trajectory (See Figure 4). The roles of bone healing is today known as Wolff’s law (Fung, 1993).

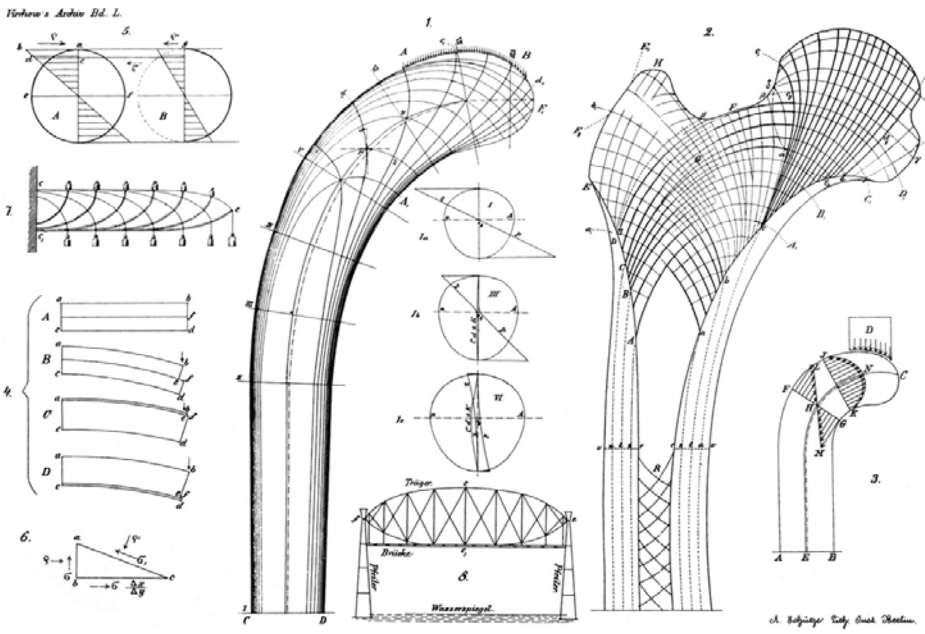

Figure 4. This figure is from J. Wolff’s 1870 paper. Part 1 shows stress trajectories in a curved Culmann’s crane and Part 2 illustrates a schematic representation of the trabecular structure of the femur (Wolff, 1870).

Bone is calcified cartilage, a composite of collagen and hydroxyapatite, $(3Ca_3(Po_4)_2 \cdot Ca(OH)_2)$ with small variations in chemical composition. Young’s modulus of the femur was measured to be 18 GPa, and for hydroxyapatite and collagen, it was measured to be 165 GPa and 1.24 GPa, respectively (Fung, 1993). This can be compared with titanium, where the modulus of elasticity is about 114 GPa (Parthasarathy *et al.*, 2010) and 225 GPa for CoCr (Sivasankar *et al.*, 2014).

Piezoelectricity is a mechanism proposed for bone healing (Fukada *et al.*, 1957), as it leads to the idea of streaming potential that may indirectly modify stiffness in bone (Ren *et al.*, 2015). Traini *et al.* (2014) draws attention to the electrical properties of collagen fibers with a band gap of 1.8eV and compares it with titanium oxides with bandgap properties of 3.20-2.96 eV. Other ideas are the biochemical activity of calcium (Justus *et al.*, 1970), and Burr *et al.* (1985) suggests that at a load of 1500 microstrains, micro fatigue occurs. The healing of the fatigue would be a part of the remodeling.

Bone tissue has the ability to heal without scar tissue. This is advantageous because it means that by using the right methodology, it is possible for a healthy person to generate fresh and healthy bone without any sign of history.

When an implant is inserted, the bone healing process will start. The blood clot is the start of the bone healing process. The blood clot is transformed into a cartilage-like callus that regenerates into woven bone with irregular fibers, which can regenerate to strong lamellar bone. The bone regenerates where mechanical load distributions appear regularly and degenerates where bone is not loaded, according to Wolff's law. The load situation between an implant and the surrounding bone is therefore very important for the long-term stability of the implant.

Blood coagulation and inflammation are early reactions. The inflammation initiates several important physiological and immune reactions which are necessary for the blood clot and bone healing (Grundnes *et al.*, 1993, Davies, 2003, Di Iorio *et al.*, 2005, Kolar *et al.*, 2010). The properties of the blood clot are also important for the subsequent bone growth. Hong *et al.* (1999) hypothesized that a coagulating, thrombogenic surface is beneficial for bone growth, but the architecture of the clot is also important. A fibrin network is formed in the clot, and the complexity of the fibrin seems to be affected by the implants' surface structure (Di Iorio *et al.*, 2005, Milleret *et al.*, 2011). Leukocytes, and later on osteoblasts, which are the cells that generate bone, will migrate onto the fibrin (Davies, 2003, Kuzyk *et al.*, 2011). The network has to stick to the surface in order for bone to be able to grow on to it, and the fibrin also has to be sparse enough for the osteoblasts to migrate through (Davies, 2007).

1.2.3 Blood

Blood is a connective tissue containing erythrocytes (red blood cells), leukocytes (white blood cells) and thrombocytes (platelets) dissolved in plasma. Erythrocytes primarily transport oxygen, are 40-45% of blood volume and are typically 7 μm in diameter (Lundh *et al.*, 2015).

Leukocytes normally occupy less than 1% of blood volume. Leukocytes are represented by lymphocytes, monocytes and granulocytes. Granulocytes are the most dominant among leukocytes, represented by basophils, which transport heparin and histamine; neutrophils, which perform phagocytosis; and eosinophils, which attack bacteria and parasites. Monocytes represent 5-10% of leukocytes. They kill and destroy through phagocytosis (Lundh *et al.*, 2015). Lymphocytes are divided into B-lymphocytes, which produce immunoglobulins, and T-lymphocytes, which kill infected cells and are natural killer cells that identify and kill alien or infected cells (Pontén, 2015).

Thrombocytes have a diameter of 2 μm and occupy less than 1% of blood volume. When they activate, they agglomerate and enhance coagulation (Lundh *et al.*, 2015).

Plasma is a water solution containing small inorganic ions such as sodium-, potassium-, calcium-, magnesium-, chloride- and bicarbonate ions, among other minerals. Plasma also contains organic substances such as proteins, carbohydrates, amino acids, fatty acids, vitamins, hormones, glucose, etc. Some important substances in plasma for the coagulation and immune system are immunoglobulins, complement proteins and coagulation factors (Lundh *et al.*, 2015).

1.2.4 Coagulation

Thrombocytes, coagulation factors (which are proteins) and fibrinogen can, under certain circumstances, activate and build a blood clot. Blood coagulation ends with a fibrin network with entrapped blood cells. Blood clots can stop the leakage of blood or start a healing process (Berséus *et al.*, 1994). A schematic representation of the blood coagulation cascade is shown in Figure 5.

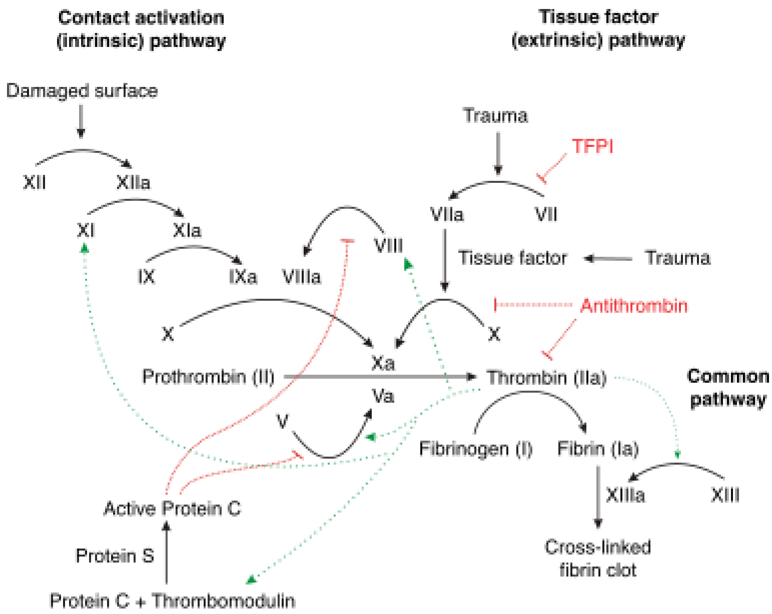

Figure 5. Schematic overview of the blood coagulation cascade.

XII, Coagulation factor XII- Hageman factor
XI, Coagulation factor XI
IX, Coagulation factor IX- Christmas factor
X, Coagulation factor X- Stuart–Prower factor
V, Coagulation factor V
TFPI, Tissue factor pathway inhibitor
VIII, Coagulation factor VIII
VII, Coagulation factor VII
XIII, Coagulation factor
XIII, Fibrin stabilizing factor
a, Activated coagulation factor

Reactions during coagulation have two pathways, the intrinsic pathway (also called contact activation) and the extrinsic pathway using tissue factor (TF). The reactions of coagulation are cascades of chain reactions.

The extrinsic pathway starts with TF, which is the only coagulation factor not dissolved in plasma. A damaged vessel wall will expose the TF to the plasma-dissolved coagulation factors (Gahrton *et al.*, 2012). TF will activate FVII, which in turn activates FX, which binds prothrombin (FII) to thrombin (Berséus *et al.*, 1994). With thrombin present, FVIII and FV get activated and thrombin formation is amplified. FVIII, together with FIX, then activates FX (Berséus *et al.*, 1994). Active FV and active FX create a feedback loop with increased thrombin formation.

The contact activation pathway starts with a conformation change of FXII adsorbed to a foreign surface as biomaterials. The active FXII activates factor XI together with high molecular weight kininogen (HMWK or HK) (Wiggins *et al.*, 1977), then FIX and then FX will be activated. The intrinsic pathway merges with the extrinsic pathway in thrombin formation.

Activated FX cleavs prothrombin to thrombin, which cleaves fibrinogen to fibrin monomer, which builds fibers and a large fibrin network with entrapped blood cells. Finally, thrombin-activated FXIII will cross link the fibrin to mesh (Berséus *et al.*, 1994).

The coagulation also contains inhibitors that, together with the coagulation factors, play a well-organized symphony. The inhibitors Antithrombin (AT), C1-inhibitor (C1-INH) and Protein C keep the clot localized and controlled (Berséus *et al.*, 1994). AT inhibits thrombin, FXII, FXI, FX and FIX. C1-INH inhibits FXII and FXI (Bäck *et al.*, 2009). Protein C inhibits FV and FVIII (Gahrton *et al.*, 2012).

2. AIM OF THESIS

This thesis is for the degree of Licentiate of Technology, and it focuses on bone to implant integration of implants manufactured using the AM technology EBM. Load-bearing implants with bone anchorage are used in dentistry, orthopedics and maxillofacial surgery.

Engineering and medicine meet in the interaction of metal implants with biology. It is important to understand the process of bone healing in order to be able to manufacture bone implants using EBM technology. This thesis has focused on some microscopic properties for surfaces and bone integration. One important macroscopic property that is not included in this thesis is anatomy-based design.

The research questions of this thesis are:

- Are untreated EBM-manufactured surfaces suitable for bone integration?
- Which process parameters are most important when considering surface roughness?
- Does the EBM-manufacturing process affect implant performance in an *in vitro* blood test system?

3. MATERIALS AND METHODS

3.1 Electron beam melting

EBM uses an electron beam to melt metal powder in a manner akin to welding. The first layer of powder is melted on top of a build plate (See Figure 6), which will be lowered according to the layer thickness to allow for the fabrication of the next layer. The remaining layers will be melted on top of each other.

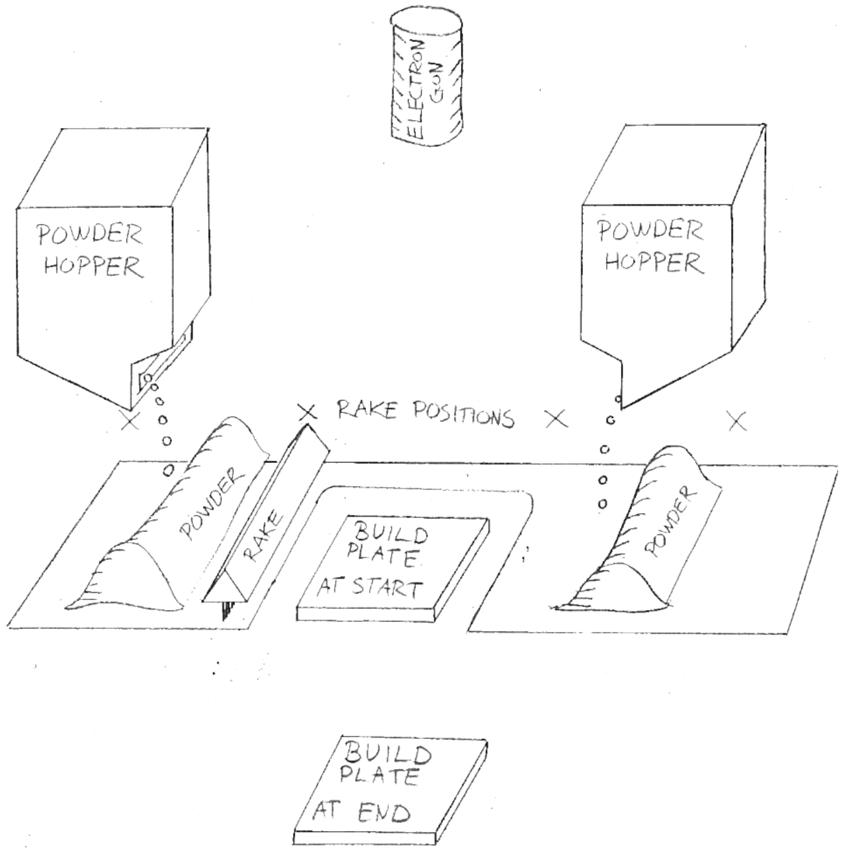

Figure 6. Schematic image of the EBM build chamber.

To manufacture one layer, the machine has to lower the start plate, deposit powder by raking and conduct preheating and melting. The melting has four main strategies, which include melting the bulk inner core, the contours, the wafer and the mesh, if present. The contours are melted separately using a default setting called MultiBeam™, which enables more than one melt pool at the same time and reduces the size of the melt pools without having to reduce input energy. The melting of the inner core is responsible for the bulk material properties. During the melting of bulk material, a lot of energy has to be transferred through previous layers. Wafer supports are extra structures used for negative surfaces and they are melted primarily to allow for heat transfer in order to prevent deformation or droplet formation. The manufacturing of mesh structures is somewhat like a structure with no bulk material and only contours. Even though melting is the process where the highest local temperature is reached, the average temperature decreases during melting and also during raking. Every cycle therefore has to contain a pre-heating step which keeps the temperature elevated during the whole build. There are algorithms built into the equipment to calculate how much pre-heating is needed to keep a good build environment.

Apart from controlling the build temperature, pre-heating has other important roles. Pre-heating will agglomerate the powder to a conducting state where the negatively charged electrons will not let the powder grains to spread away. Pre-heated powder conducts electricity to a certain extent and also thermally insulates.

There are hundreds of process parameters that control the manufacturing process that operators can change. Some examples of parameters that control the contours are: number of contours, beam speed, beam current, offset to other structures, beam focus offset, whether or not all contours should have the same setting, turn on/off MultiBeam™, turn on/off contours, etc. Layer thickness and powder properties will also influence the properties of a product, as will build environmental properties such as degree of vacuum, raking and the build temperature.

3.2 Materials

3.2.1 Titanium

There are three different grades of titanium available for EBM: grade 2, CP-titanium; grade 5, Ti6Al4V; and grade 23, Ti6Al4V-ELI. Their chemical compositions and material properties are presented in Tables 1-6. The bulk material of EBM products is fully melted, which makes the material properties better than those of sintered materials and comparable to those of cast and wrought products. The microstructure contains fine grains because the electron beam keeps the melt small and solidification may occur at a small volume at a time. The elevated temperature during the build and slow simultaneous global cooling favors EBM products in avoiding inner tensions (Svensson *et al.*, 2009). Chemical compositions and static tensile test data complies with ASTM standards (Svensson *et al.*, 2009).

Hot isostatic pressing (HIP) is recommended at 920°C, 1000bar for 2h to improve the fatigue resistance (Svensson *et al.*, 2009).

From room temperature to 882°C, titanium has CHP α-form and BCC β-form at higher temperatures. Hydrogen interstitials are β-stabilizers, while carbon, nitrogen and oxygen are α-stabilizers. Aluminum is a strong α-stabilizer to titanium. Titanium with vanadium or iron (Fe) will have precipitates with an embrittling ω-phase.

Table 1. Chemical specification of Ti6Al4V-ELI, grade 23 (Arcam AB)

	Arcam Ti6Al4V ELI*	Ti6Al4V ELI Required**
Aluminum, Al	6.00%	5.5–6.5%
Vanadium, V	4.00%	3.5–4.5%
Carbon, C	0.03%	<0.08%
Iron, Fe	0.10%	<0.25%
Oxygen, O	0.10%	<0.13%
Nitrogen, N	0.01%	<0.05%
Hydrogen, H	<0.003%	<0.012%
Titanium, Ti	Balance	Balance

*Typical, **ASTM F136

Table 2. Mechanical properties of Ti6Al4V-ELI, grade 23 (Arcam AB)

	Arcam Ti6Al4V ELI*	Ti6Al4V ELI Required**
Yield Strength (Rp 0.2)	930 MPa	795 MPa
Ultimate Tensile Strength (Rm)	970 MPa	860 MPa
Rockwell Hardness	32 HRC	30–35 HRC
Elongation	16%	>10%
Reduction of Area	50%	>25%
Fatigue strength @ 600 MPa	>10,000,000 cycles	>1,000,000 cycles
Modulus of Elasticity	120 GPa	114 GPa

*Typical, **ASTM F136

Table 3. Chemical specification of Ti6Al4V, grade 5 (Arcam AB)

	Arcam Ti6Al4V, Typical	Ti6Al4V,Required*	Ti6Al4V, Required**
Aluminum, Al	6%	5.5–6.75%	5.5–6.75%
Vanadium, V	4%	3.5–4.5%3	0.5–4.5%
Carbon, C	0.03%	<0.1%	<0.08%
Iron, Fe	0.10%	<0.3%	<0.3%
Oxygen, O	0.15%	<0.2%	<0.2%
Nitrogen, N	0.01%	<0.05%	<0.05%
Hydrogen, H	0.00%	<0.015%	<0.015%
Titanium, Ti	Balance	Balance	Balance

*ASTM F1108 (cast material), **ASTM F1472 (wrought material)

Table 4. Mechanical properties of Ti6Al4V, grade 5 (Arcam AB)

	Arcam Ti6Al4V,Typical	Ti6Al4V,Required **	Ti6Al4V,Required **
Yield Strength (Rp 0.2)	950 MPa	758 MPa	860 MPa
Ultimate Tensile Strength (Rm)	1020 MPa	860 MPa	930 MPa
Elongation	14%	>8%	>10%
Reduction of Area	40%	>14%	>25%
Fatigue strength* @ 600 MPa	>10,000,000 cycles		
Rockwell Hardness	33 HRC		
Modulus of Elasticity	120 GPa		

*After Hot Isostatic Pressing, **ASTM F1108 (cast material), ***ASTM F1472 (wrought material)

Table 5. Chemical specification of Titanium, grade 2 (Arcam AB)

	Arcam Titanium, Grade2, Typical	Titanium Grade 2, Required*
Carbon, C	0.01%	<0.08%
Iron, Fe	0.05%	<0.3%
Oxygen, O	0.19%	<0.25%
Nitrogen, N	0.00%	<0.03%
Hydrogen, H	0.00%	<0.015%
Titanium, Ti	Balance	Balance

*ASTM F67 (Unalloyed Titanium for Surgical Implant Applications)

Table 6. Mechanical properties of Titanium, grade 2 (Arcam AB)

	Arcam Titanium, Grade 2, Typical	Titanium Grade 2, Required*
Yield Strength (Rp 0.2)	540 MPa	275 MPa
Ultimate Tensile Strength (Rm)	570 MPa	345 MPa
Elongation	21%	>20%
Reduction of Area	55%	>30%

*ASTM F67 (Unalloyed Titanium for Surgical Implant Applications)

3.2.2 Cobalt Chromium

The Cobalt Chromium (CoCr) alloy commercially available for EBM is ASTM F75, which is a common CoCr alloy composition for medical implants. It is used for medical implants because of its high stiffness, wear resistance and resistance to fatigue, which is one of its most important properties. Polishing allows for a mirror-like finish (Arcam AB, 2011).

As-built microstructures have long grains in the build direction, i.e., the z-direction, with carbide precipitations. As-built material has a high hardness (Arcam AB, 2011).

HIP and HOM treatment will transform the microstructure to an isotropic structure where the carbides are saturated in the grains, which increases ductility and fatigue resistance (Arcam AB, 2011). The recommended HIP for CoCr is at 1200°C, 1000 bar argon for 2h and HOM at 1220°C, 0.7-0.9 mbar argon for 2 h, which should be followed by a rapid quench.

Table 7. Mechanical properties CoCr ASTM F75(Arcam AB, 2011)

	Arcam, as-built*	Arcam, after heat treatment	ASTM F75-07, *required
Rockwell Hardness	47 HRC	34 HRC	25–35 HRC
Tensile Strength,		960 MPa	655 MPa
Ultimate		140,000 psi	95,000 psi
Tensile Strength,		560 MPa	450 MPa
Yield		80,000 psi	65,000 psi
Elongation at Break	Not applicable	20%	>8%
Reduction of Area	Not applicable	20%	>8%
Fatigue limit, Rotating		>10 million cycles, 610 MPa (90 ksi)	

*Typical

Table 8. Chemical specification of CoCr ASTM F75 (Arcam AB, 2011)

	Arcam ASTM F75*	ASTM F75 Required
Chromium, Cr	28.50%	27–30%
Molybdenum, Mo	6%	5–7%
Nickel, Ni	0.25%	<0.5%
Iron, Fe	0.20%	<0.75%
Carbon, C	0.22%	<0.35%
Silicone, Si	0.70%	<1%
Manganese, Mn	0.50%	<1%
Tungsten, W	0.01%	<0.2%
Phosphorus, P	0.01%	<0.02%
Sulphur, S	0.01%	<0.01%
Nitrogen, N	0.15%	<0.25%
Aluminum, Al	0.05%	<0.1%
Titanium, Ti	0.01%	<0.1%
Boron, B	0.01%	<0.01%
Cobalt, Co	Balance	Balance

*Typical

3.3 Surface characterization

There are many different kinds of equipment that can conduct surface characterization and there are many ways of using the same equipment. It is also important to understand the physiochemical and mathematical impacts on the results. Scanning electron microscopy (SEM), atomic force microscopy (AFM) and stylus profiler are just a few techniques. AFM and profilometry are tactile methods, while SEM is a non-tactile method. Tip diameter or wavelength and scan area are the obvious limitations on the detection window.

R_a was characterized with a surface profiler (Dektak® 6M (Veeco, USA)). The tip diameter was 25 µm. The tip was dragged perpendicularly to the lays, parallel to the build direction. The scan length was 2 mm and each specimen was measured eight times, and the R_a value presented are mean values from those scans. R_a was calculated with the profiler software and exported to MATLAB (R7.11.0, The MathWorks Inc., USA).

3.3.1 Average surface roughness

The average surface roughness R_a is defined by Eq. 1.

$$R_a = (1/L)\int_0^L |Z(x)|dx \qquad (1)$$

R_a is the integral over the surface profile Z of x over the distance L, where x is the variable going from 0 to L. Average surface roughness is normalized by dividing by the length of the surface profile L.

3.4 Design of experiment

Design of experiment (DOE) is a method on how to set up the experiments in order to get as much information on the system as possible. DOE also gives information on the correlation between parameters which, in some cases, is as important as single process parameters. Paper II used a 4^2 experiment DOE set-up, which was full factorial. In this thesis, the surface roughness was evaluated as the response and the factors were process parameters controlling the electron beam. Theory in DOE tells how to set up the parameters to get as much information as possible with a limited number of trials. The results are compared and the statistical differences of the results will tell how much a process parameter affects the surface roughness in terms of probability (Montgomery, 2005).

3.5 In vitro evaluation

3.5.1 Blood chamber model

The blood chamber model is an *in vitro* method that uses human whole blood to identify the early reactions important for later stages of bone healing (Hong *et al.*, 1999). Using biochemical analysis, it is possible to identify which blood and immune reactions have started upon exposure to a surface specimen. Using that information, we can estimate the architecture of the blood clot and possible occurrence of bone formation. There is a hypothesis that fast blood coagulation is an indication of fast bone healing (Hong *et al.*, 1999, Thor *et al.*, 2007). Whole blood is unmodified, and in these experiments it has not been stored before coming into contact with the surfaces in question.

The chambers and the metal surface samples, which will serve as lids or walls in the blood chamber, were prepared in the following manner. All material in contact with blood, such as tubes and chamber surfaces, that were not the test surface, were coated with a heparin conjugate (CHS™ Corline heparin surface) which is an anticoagulant that mimics heparin sulfate proteoglycans naturally found on the inside of blood vessels, which are not supposed to activate blood coagulation (Lundh *et al.*, 2015). Human blood partially anti-coagulated with heparin was collected and used within 20 minutes and reference blood samples were set aside, blocked with EDTA. Heparin was added to the blood, which slows down the initial blood reactions to enhance the resolution of early reactions. After the addition of blood into the chambers, the metal surface samples were secured onto the chambers, which were incubated in a heat cabinet at 37°C to mimic a physiologic environment under rotation for 30 minutes, which gives the blood turbulence to which it normally would be subjected. Every chamber then contained an entrapping environment where coagulated blood stuck to the metal samples and a blood solution was left in the chambers. After the experiment, EDTA was added to the blood to freeze all immunoreactions and a blood cell count was conducted using a cell counter that identifies blood cells according to size. Then blood samples were centrifuged to separate the plasma from the blood cells. Plasma was then stored at -70°C for further analysis, such as ELISA.

3.5.2 Enzyme-linked immunosorbent assay

Enzyme-linked immunosorbent assay (ELISA) may be used to quantify factors, proteins or other subjects that are dissolved in blood plasma. ELISA uses antibodies with only target-specific antigens (subjects) by strong bonding. By selecting antibodies by their antigen target, they can be used to connect illuminating molecules such as a blood factor. The color brightness may then be translated to blood factor concentration.

The contact system activation-generated complexes "FXIIa-AT," "FXIa-AT," "FXIIa-C1-inh" and "FXIa-C1-inh" were measured by sandwich ELISA (See Figure 7, which depicts Steps 1 to 5). In Step 1; microtiter wells were covered with Anti-Human FXII antibodies or Anti-Human FXII antibodies. In Step 2; plasma samples were put into the wells and the coagulation factors bonded to the wells. In Step 3; the microtiters were then washed. In Step 4, antibodies to antigen AT or C1-inh were added to the wells as secondary antibodies, then the microtiter were washed again. The secondary antibodies were biotinylated and detected using streptavidin-HRP. Chromogen 3,3′,5,5′-Tetramethylbenzidine (TMB) was added and the reaction was halted by the addition of acid. In Step 5; the absorbance at 405 nm was read and assumed to be proportional to the coagulation factor-inhibitor complex concentration (Sanchez *et al.*, 1998).

For the Thrombin-Antithrombin complex, microtiter wells were coated with Anti-Human thrombin antibodies. Bound complexes were detected with HRP-conjugated anti-human antithrombin antibodies.

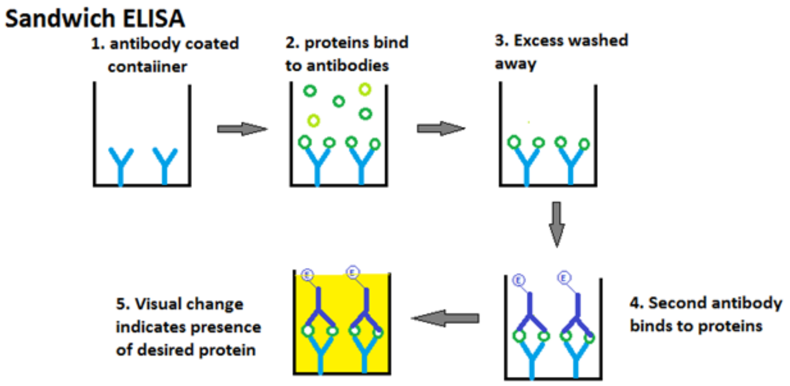

Figure 7. Schematic image of how layers of antibodies and antigens are stacked in sandwich ELISA. (Wikimedia Foundation. Inc.)

4. RESULTS

4.1 Paper I

This paper discusses the possibilities, challenges and limitations for electron beam melting as an implant manufacturing technology. Potential outcomes are implants with properties of amorphous metal and porous mesh-structures that may be designed and integrated with solid structures, which could be used for customization. Other topics are chemical or electrochemical post-processing to remove certain structures from the surface. On the millimeter to macro scale, beams in a mesh structure may not be smaller than 0.2-0.5 mm. Smaller limitations in surface appearance are claimed to be affected by powder size, process parameters and melt pool size. My contribution to this paper were some results from my master thesis where initial experiments of EBM-manufactured CoCr surfaces had been evaluated using the blood chamber model with satisfying results in thrombogenicity.

4.2 Paper II

In Paper II, the *in vitro* blood chamber model was used to evaluate CoCr samples. The result shows that blood coagulation occurs in a way that is needed for bone ingrowth. The EBM-manufactured samples with process parameters using no contours with mean R_a=35 µm showed a tendency to more thrombocyte activation than those manufactured with contour settings Mean R_a=28.2 and 28.5 µm. The samples had R_a of 25-40 µm, which is considered to be a very rough to porous surface topography.

4.3 Paper III

In Paper III, a set of process parameters that were assumed to have an impact on surface roughness were selected. DOE was used to minimize the number of trials and the response using R_a showed that process parameters have an impact on the surface properties. The most prominent parameter to have an impact on the surface roughness was the combination of speed and current.

EBM products have a surface structure originating not only from the layer thickness, but also from metal powder grains partially melted and partially sintered to the surface. The main role of the surface roughness in this study is to compare surface roughness using different process parameters within this study and the second role was to compare size range with other studies.

4.4 Paper IV

Paper IV aims at showing EBM as a feasible manufacturing tool for implant manufacturing. A lot of additively manufactured implants have been implanted during the last decade, but there is still a need from the industry for more research in topics such as long-term evaluation of osseointegration and methods for evaluating the possibilities of new materials and surface structures. The titanium samples in this study were selected from the specimens manufactured for Paper III, which were used for experiments using the blood chamber model. The selection was conducted according to R_a rather than process parameter. EBM-manufactured specimens had R_a of 18.6-25.0 μm, 29.7-37.1 μm and 41.2-45.6 μm, while the reference had R_a=1.73 μm. The results show that blood coagulation is significantly higher on the EBM-manufactured surfaces compared with the machined titanium surfaces.

Paper IV did not discuss porosity or mesh structures, but its purpose was rather to show the feasibility of EBM as a manufacturing technique for implants. Mechanisms of bone healing are handled more deeply in Paper IV than in Paper II. For example, inflammatory reactions in bone healing were highlighted.

5. DISCUSSION

5.1 Size range

There is a large scope in size range from macro to the nano level associated with implants, physiological reactions and bone ingrowth, which is discussed as it might have an impact on performance. At the nm to Å size range, we can find the size of atoms and molecules, where electric potentials are generalized and described using chemical bonds. The bonding between bone and the implant oxide layer is not defined, but the piezoelectric effect (Fukada *et al.*, 1957) and band gap (Traini *et al.*, 2014) are discussed as relevant to bone ingrowth in the literature.

The sizes of protein-signaling substances and coagulation factors can be approximated by assuming that one atom is 0.1 nm = 1 Å. The peptides have various sizes, but the peptide bonding would be approximately 3 atoms long. Given that the active site on an immunoglobulin is 6 amino acids in a row, which would make the active site approximately 18 Å ≈ 2 nm.

The composition of blood cells and plasma protein in blood changes quickly, and the composition described above is only a generic composition in a healthy person. The coagulation cascade and complement systems are made of chain reactions whose primary purpose, together with the immune system, is to stop whatever is trying to harm the inner body environment. There are also other plasma proteins, enzymes and signaling substances in the cell membranes and in plasma to elucidate, and the chain reaction charts will likely be updated in the near future. In the experiments set out in this thesis, the set of process parameters were able to vary the surface roughness between 20-50 μm. If a soluble molecular component has a chemical reaction with the surface, one can hypothesize that the reaction rate would be directly proportional to the total surface area, which was investigated in Paper IV.

A powder grain is about ten times bigger than a blood cell. It is not fully understood if the first thrombocyte that binds get stuck in a notch or if it sit on a certain nanostructure, and then whether the second one sticks on top of the first one, or if it sit next to the first one at the surface. There are structures on micro and nano levels that might have a physical impact that could affect the surface-implant interface. The increase of surface roughness at titanium from 1,5 nm to 425,7 nm was shown by Hong *et al.* (1999) to cause significant increase of contact activation of coagulation. In addition a study by Ferraz *et al.* (2010) showed that surface structures in the size of 20 nm respective 200 nm affects blood coagulation properties differently.

The shape and fitting of a customized implant can be achieved with a precision in the range 0.1-1 mm. Mesh structures may be designed with pores larger than the metal powder grains. By using mesh structures it is possible to manufacture metal structures with lower moduli of elasticity, closer to that of bone. Capillary action due to friction and chemical bonding may keep a large blood volume entrapped, which would stimulate coagulation that occurs in non-turbulent (i.e., still) blood.

Bulk structures and mesh structures are melted with different EBM process settings, likely due to the scale/size effect. The melt pool energy, which is proportional to volume, has to escape through the bottom or through the walls of which sizes are proportional to area. Due to scale, the volume and area change by the power of 3 and 2, respectively. Safdar *et al.* (2012) showed that the thickness of a sample affects the surface roughness.

If the powder size were changed from the current size of 45-100 μm to, for example, 25-45 μm, the surface resolution would be improved (Karlsson, 2015). Smaller powder size also gives better conditions for thinner layers. The EBM process gives fully melted material properties because the melt pool reaches through about three layer of thickness. The size of the melt pool has an impact on grains in the microstructure (Thijs *et al.*, 2010), which is why the melt pool should also have an impact on surface properties too. The former layer thickness was 100 μm, Studies II, III and IV were conducted using 70 μm layers, and currently there are process settings with 50 μm layers.

In the long term, in a macro perspective, the goal is to have an even load distribution over the whole surface-implant interface and the bone cross-section. To achieve that, it is important to consider the rigidity of the implant and the surrounding bone, and the material properties should be optimized to maintain, support and generate new bone.

5.2 Material properties

EBM products have a surface structure originating from metal powder grains partially melted and partially sintered to the surface. For commercial cement-less implants, a surface structure is often added using, for example, sputtering to enhance bone anchorage (Pilliar, 2005). Yang *et al.* (2014) showed by using an animal model that EBM-manufactured screws show good properties for bone ingrowth and suggest that no surface treatment is needed for titanium implants with bone anchorage.

Porosity and porous materials have not been discussed deeply in any of the papers in this thesis. However, porosity has been an important issue, and this work was considered to build a knowledgebase in the area of EBM and will be used as a foundation for further research. Kelly (2006) suggests introducing pores to titanium to reduce its stiffness to reduce the stress shielding effect.

To convince the market that AM can compete with conventional manufacturing, process parameters have been optimized to manufacture material properties according to conventional manufacturing standards. New AM applications are being developed quickly and standards are being developed by authorities to meet these new demands.

Pilliar (2005) explains how conventional implants with sintered metal beads have impaired material properties due to microstructural grain growth due to the sintering temperature treatment, and Kuzyk *et al.* (2011) state that mechanical strength is inversely proportional to microstructural grain size. EBM materials with metal beads on the surface have not undergone sintering temperature treatment. The powder grains were melted or fused in place using the electron beam during bulk material manufacturing in the weld-like strategy. The melt pool is kept small, which allows melting and solidification to occur quickly and at a small volume, which results in finer microstructure compared with products manufactured using casting or forging. Post-temperature treatments are often recommended for metal implants manufactured using EBM technology, which does impact the microstructure and material properties, but this treatment is designed to improve the material performance. After heat treatment, the EBM-CoCr alloy will go from 47 HRC to 34 HRC in hardness which is still in the upper boundary of the ASTM F75 requirement (25-35 HRC), and its ductile properties will increase, which will resist fatigue, as its fatigue limit will be 610 MPa at 10^7 cycles (Arcam AB, 2011). After HIP, Ti6Al4V shows small changes in yielding and ultimate strength (Svensson *et al.*, 2009), which indicates small changes in hardness. The fatigue limit, which is related to ductility, is also increased, where as-built fatigue limit is 257-296 MPa at 10^7 cycles, and HIP-treated has 518 MPa at the same amount of cycles (Svensson *et al.*, 2009).

5.3 Surface resolution

The powder size of EBM powder was set to a minimum size due to risk of ignition. Karlsson (2015) investigated smaller powder sizes and found that it is possible to manufacture, provided good care is taken. Karlsson (2015) also investigated oxidation and the chemical composition of surfaces manufactured with smaller powder size and found no significant deviations from products manufactured with standard powder size. It is important to conduct further research on surface characteristics to be able to meet the demands in surface resolution step by step. As long as EBM will use metal powder as raw material, the surface will have traces from it. Since AM is going to be more accepted as time goes on, the new surface will extend the current concept of a "normal" surface. The strength in AM is its core bulk properties in combination with its design geometry. The surface will have to be a secondary property, unless there are applications where surface roughness enhance the functionality. Fatigue failure due to irregularities in the surface is, however, an engineering issue that must be taken seriously.

5.4 Titanium

Titanium is today known as a thrombogenic material (Hong *et al.*, 1999, Thor *et al.*, 2007). However, authors have mentioned inertness as being positive for orthopedic implants. Bobyn *et al.* (1980) pointed to inertness as an important factor for biocompatibility. Kelly et al (Kelly, 2006) mentions inertness and lack of inflammatory reactions. In Paper IV, some physiological reactions, such as coagulation and inflammation, are discussed, as they are important for bone ingrowth, and those reactions are what the blood chamber model uses as indicators as to whether bone growth would have good conditions to proceed in the coagulated blood.

Titanium implants have been used in heart pumps and heart valves, but one of the problems is that patients with artificial heart prostheses have increased risk of thrombotic events and need anticoagulant therapy (Hong *et al.*, 1999, Smallman *et al.*, 1999, Kounis *et al.*, 2014). In vitro experiments using plasma have showed little reaction in contact with titanium, but experiments using whole blood exhibit thrombocyte activation leading to blood coagulation. In 2015, titanium is still designated as a bioinert material in several publications (Rudnev *et al.*, 2014, Yue *et al.*, 2014). Titanium is however considered hypoallergenic and recent studies have shown a low prevalence in titanium allergy (Sicilia *et al.*, 2008).

Titanium and titanium alloys used for implants have the same titanium oxide coatings, their behavior is likely to be similar, and the reports so far would indicate that the titanium alloys are equally as biocompatible as CP-titanium (Van Noort, 1987). It is not well-declared in literature which alloy composition has been used in studies involving titanium implants. Out of the ten article hits on "titanium implant", four were not well-declared (Ayton *et al.*, 2014, Li *et al.*, 2014, Taha *et al.*, 2014, Koch *et al.*, 2015), three used CP-Titanium (Kim *et al.*, 2014, Windolf *et al.*, 2014, Chen *et al.*, 2015), two used titanium alloys (Kafkas *et al.*, 2014, Smith *et al.*, 2015), and one was not about metal implants (Giannini *et al.*, 2014).

Ti6Al4V-ELI has been used for medical implants due to its strength, corrosion resistance, ductility (workability) and its damage tolerance (Smallman *et al.*, 1999), but other important material properties may be promoted with pre-operative planning in combination with AM. New material compositions for EBM manufactured products do not have to withstand cold work, i.e. bending, which means that ductility will not have to compromise on strength in the same manner as does conventional manufacturing. AM has shown its abilities to manufacture implants with the same shape and material properties as those manufactured using conventional techniques, using material compositions optimized for cast and wrought production. Material compositions in the future may be more optimized for AM production and implant performance.

Vanadium has also been questioned as a toxic agent (Walkowiak-Przybyło *et al.*, 2012). Other titanium alloys could be more suitable for medical implants and EBM manufacturing. Wang *et al.* (2013) suggests titanium-indium as dental biomaterial.

5.5 Surface characteristics

How to characterize surface topography on metallic implants is a well-discussed topic. The method used will impact the given result, and which surface parameter is used will influence the specific information about the surface. R_a, for example, only gives information about the amplitude and gives no information about frequency.

Surface parameters are seldom comparable from article to article (Wennerberg *et al.*, 2009), but still the most widely used surface parameter is R_a, which is basically an average height-depth value.

In most cases, EBM surfaces will not have the same shape as conventional products. Similar to cast products that have marks from the mold, AM products will have a staircase structure from the layers and tracks from the raw material. However, post-processing can give any conventionally designed AM product the same surface finish as products manufactured by conventional methods. The limit in surface finish is that complex geometries might have surfaces in angles where the conventional surface processing method does not reach.

6. CONCLUSIONS

EBM-manufactured surfaces have an as-build surface with porous structure similar to those described by Pilliar (2005) and (Kuzyk *et al.*, 2011), but without impaired bulk material properties because the products have not been sintered. In Papers I, II and IV, the blood chamber model shows that as-built EBM manufactured surfaces have thrombogenic properties which, in previous studies, is correlated with bone ingrowth (Hong *et al.*, 1999, Thor *et al.*, 2007).

The EBM process parameters affect the surface properties. For finer surfaces, thinner layers and finer powder will increase the theoretical resolution , and the process parameters may be optimized to such conditions (Karlsson, 2015). The process parameters in the default settings are set according to, for example, powder properties, layer thickness and also parameters has to be in harmony with each other. Using the contour setting compared to using no contour setting has a large impact on the surface properties. The set of parameters investigated in Paper III shows that the combination of speed and current had the most impact on the contours.

EBM manufacturing has shown its feasibility to manufacture products with bulk material properties comparable to those of products manufactured by conventional techniques. Surface processing can give EBM products equal properties as conventional implants using the same material composition and processing technique (Karlsson, 2015). Still, there is a lot of room for improvement to optimize the EBM manufacturing process to target specific applications, and products may have geometry improvements beyond the limits of conventional subtractive or formative manufacturing. The advantages of AM implants are having more degrees of freedom in the design and customization in terms of, for example, geometry and porous material with designed stiffness. EBM can manufacture geometries with angles that commonly were manufactured by bending without having to be subjected to cold work or other post heat treatment (other than HIP and HOM). Implants can be manufactured with combinations of mesh and bulk material.

The as-built surface does have a negative impact on fatigue resistance, and more research will have to be conducted on this topic. One way to overcome this problem is to combine polished and as-built surfaces by making sure that the weak spots, i.e., those with high stress deviations, have a polished surface.

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